Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/622,646	OZAKI ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 June 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,6-9,13 and 17*.
   Claim(s) withdrawn from consideration: *3,4,10-12 and 14-16*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☒ Other: Note the attached form PTO-892.

/Christine Foster/
Examiner, Art Unit 1641

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

Continuation of 5. Applicant's reply has overcome the following rejection(s): The objections to claims 1 and 17 have been withdrawn in response to Applicant's amendments thereto.

Continuation of 11. does NOT place the application in condition for allowance because:

Applicant's arguments with respect to the rejections of claims 1-2, 6-7, 13, and 17 under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Ishikawa et al. , Gastinel et al., Lauffer et al., Laping et al., and Lo et al. have been fully considered (see Reply, pages 6-8) but are not persuasive.

Applicant argues that one skilled in the art would not be motivated to remove the Fc sequence for use in detecting soluble HM1.24 antigen because as provided in the prior art, the purpose of fusing Bst-2 (HM1.24) to an Fc sequence is "to form a dimer…so as to improve and enhance the pharmacokinetic properties (especially stability, half-life, activity, etc.)". Applicant further argues that removal of the Fc region would be counter to what the ordinary artisan was trying to achieve, namely a more stable HM1.24 protein for detection of soluble HM.24 antigen protein at low concentrations.

Initially, it is noted that Applicant refers to methods for detecting soluble HM1.24 antigen "protein". The relevance of such arguments in the context of the instant claims, which are directed to an assay for detecting anti-HM1.24 antibody, is not clear.

Nonetheless, Applicant's arguments that one would not be motivated to remove the Fc domain of the HM1.24 antigen are not persuasive for the following reasons. In particular, the Office has contended that it would have been obvious to employ a soluble form of the HM1.24 antigen, i.e. an HM1.24 antigen lacking the transmembrane domain. Although one possible way of obtaining such a soluble form would be to produce the soluble HM1.24 antigen as an Fc-fusion protein and subsequently remove the Fc domain, this was mentioned only as an exemplary means of obtaining a soluble form of the HM1.24 antigen. As taught by Gastinel et al., soluble antigens can be produced simply by removing the transmembrane domain.

The prior art therefore teaches that it was generally known to use soluble forms of receptors without their transmembrane domains, and this general teaching is not limited only to receptors initially produced as Fc fusions. For these reasons, the issue of patentability cannot be decided simply by assessing whether one would be motivated to remove an added Fc sequence.

Notwithstanding the above, Applicant's arguments that one would not be motivated to remove an Fc sequence are not persuasive. Applicant argues that the prior art used such sequences for the purpose of dimerization, but does not indicate where this teaching is found in the evidence of record.

In addition, Applicant argues that Fc sequences were used to improve and enhance "pharmacokinetic properties", and points to attached Exhibit A. Applicant argues that one would not remove the Fc sequences since such advantages would not accrue.

This is not found persuasive because the claimed invention is directed to an in vitro method for assaying anti-HM1.24 antibody. Applicant's arguments regarding "improved pharmacokinetic properties" relate to the in vivo use of Fc-containing proteins as pharmaceutical agents. Applicant has not provided any reasoning as to why in vivo pharmacokinetic properties would be desirable or even relevant when using proteins for in vitro uses.

To the contrary, it is noted that those of ordinary skill in the art recognized that for in vitro diagnostic applications such as the instantly claimed methods, the presence of Fc sequences may be detrimental.

For example, and solely to address Applicant's remarks in this regard, Matsuzawa et al. (U.S. 5,374,533 recognized that nonspecific interactions can occur between Fc sequences and components in a sample such as rheumatoid factor, which results in nonspecific interactions in immunoassays. See column 2, lines 9-32. To avoid this problem of nonspecific interactions, the authors removed the Fc sequence from their immunoassay reagent (in this case, an antibody). See also column 4, lines 41-55.

Therefore, while Fc sequences may have been recognized to have a functional role in vivo, the prior art recognized that such sequences may result in nonspecific binding in in vitro immunoassays. For these reasons, Applicant's arguments that one of ordinary skill in the art would not seek to remove the Fc domain are not found persuasive.

Applicant further argues that it was newly found that a soluble HM1.24 antigen can form a dimer without the addition of an Fc sequence (Reply, page 7). This is not found persuasive because the instant claims do not recite or require that the HM1.24 antigen be dimeric. In addition, the examiner was unable to find any teaching in Appendix A which states that the Fc region is used for the specific purpose of preparing a protein in dimeric form. Consequently, whether or not the ordinary artisan would have expected a soluble HM1.24 antigen protein to be dimeric without the transmembrane domain and without an Fc tag is seen as tangential to the determination of obviousness.

Applicant acknowledges that the Laping reference describes removal of the Fc region, but argues that this is in the context of where the antigen is used for immunization (Reply, page 8, first paragraph). Applicant argues that by contrast, the presently claimed invention is directed to a soluble protein used as an antigen for measuring an antigen, and not as an antigen for immunization (Reply, page 8).

This is not found persuasive because as noted above, the instant claims are directed to a method for assaying an antibody and not an antigen. Moreover, the teaching of Laping et al. to which Applicant points clearly indicates that applications where the protein are used for immunization is an example of one case where it is desirable to remove the Fc portion. When read as a whole, Laping et al.

contemplate multiple situations where it is desirable to do this, as is not limited to the particular application noted by Applicant. See also the discussion of Matsuzawa et al. above, which indicates that the general knowledge in the art included the recognition that Fc sequences may interfere in in vitro immunoassays.

For all of these reasons, Applicant's arguments that one of ordinary skill in the art would not have been motivated to arrive at the claimed invention because removal of Fc sequences would be viewed as undesirable are not persuasive.

Applicant does not separately argue the limitations of dependent claims 8-9 (see Reply, page 8).